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14. ABSTRACT
PURPOSE/SCOPE: Over 50% of screen-detected men with low-risk prostate cancer (CaP) are overtreated, and treatment is associated with significant adverse effects (AE). This analysis examines the cost-effectiveness of radical prostatectomy (RP), radiation therapy (IMRT), and brachytherapy (BT) compared with active surveillance (AS) (followed by IMRT if treated) in these men. METHODS: A Markov Monte Carlo model was constructed: AE of treatment were included. Main outcomes were costs (2008US$), quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs) for men 65, 55, and 75 years of age. RESULTS: AS was most effective at all ages studied. In 65 yo men, it provided 8.38 QALYs at a lifetime cost of $34095. Compared to BT, AS provided an additional 4.2 mo of QALE at an added cost of $3,883 (ICER $11094/QALY). BT was the most effective and least expensive initial therapy, providing an additional 2.5 mo of QALE at a cost savings of $3086 vs. RP. AS was most effective on sensitivity analyses including probability of AE, progressive disease on AS and utilities, and remained cost-effective at all ages analyzed and on all sensitivity analyses. CONCLUSIONS: In this model, AS is a cost-effective alternative to initial treatment in men 55-75 in all scenarios analyzed. AS is underutilized in men with screen-detected, low-risk disease.

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Prostate cancer, screening, cost-effectiveness analysis

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INTRODUCTION

This annual report details the progress that has been made between August 2010 and August 2011, the second year of the Physician Research Training Award entitled "Decision analysis of the benefits and costs of screening for prostate cancer". The goal of the proposed research is to develop a decision analytic model of PSA screening for prostate cancer. This model will permit the analysis of the effect of various PSA screening strategies on life expectancy (LE), quality-adjusted LE (QALE), and the cost-effectiveness of screening. The comparator will be a natural history model of unscreened, conservatively-treated prostate cancer based on primary data unique in its duration of follow up and inclusion of Gleason scores from the modern era. It is hypothesized that the optimal screening strateg(ies) for prostate cancer will be dependent not only upon mortality benefit, but also upon the value patients place on health states and costs.

This report will summarize the accomplishments that have been made in undertaking the tasks outlined in the Statement of Work. Due to difficulties that have arisen in conducting Task 1, described in the body of this report, the majority of the work conducted to date has been on Task 3. The portion of the model described in Task 3 assesses the life expectancy, quality-adjusted life expectancy, and cost-effectiveness of treatment in screened vs. unscreened men with prostate cancer. Over the past two years, a model has been constructed comparing first the effectiveness, then the cost-effectiveness of treatment strategies for low-risk, clinically localized prostate cancer. The strategies modeled included active surveillance, radical prostatectomy, brachytherapy, intensity-modulated radiation therapy, and proton beam therapy. It was found that active surveillance is the most effective treatment, or associated with the greatest quality-adjusted life expectancy, but brachytherapy is the least expensive treatment. Active surveillance remains cost-effective under all scenarios constructed and in men aged 55 to 75. Results of this model have been published in the *Journal of the American Medical Association,* presented at annual meetings of professional societies, discussed in a teleconference sponsored by the Institute for Healthcare Improvement and *JAMA,* and discussed at the Cancer Intervention and Surveillance Modeling Network's (CISNET) Annual Conference at the National Institutes of Health. A second manuscript arising from this model is currently in its final stages of preparation, and a third is being written.

This report will also summarize the training accomplishments achieved over the past year. As planned, I have received extensive training in the construction and population of a Markov Monte Carlo model, I have attended and presented at professional society annual meetings, participated and presented in institutional conferences, and pursued coursework. I have participated in meetings with my mentors as planned.

Although the order in which the work is being conducted has changed due to circumstances beyond my control, the tasks outlined in the original statement of work will be performed as originally planned. I look forward to the opportunity to continue working on this timely and important work.

BODY

TASK 1: Develop a Markov Monte Carlo disease model of the natural history of prostate cancer.

Methods. We will create a Markov Monte Carlo disease model of the natural history of prostate cancer. Individuals will progress from a disease-free state to preclinical disease to clinically-detectable prostate cancer; each individual will have a PSA value and, in those with prostate cancer, a Gleason score. Men with disease will progress from clinically localized to regional to metastatic disease and death of prostate cancer; they may also progress between Gleason scores. Death of other causes can occur from any health state.

Task 1.1 Utilizing data from the published literature, create a model of the preclinical development of prostate cancer. Estimates of age-specific prevalence of preclinical prostate cancer, correlation of the presence of preclinical disease with serum PSA, and evaluation of PSA rise in the serum of patients subsequently diagnosed with prostate cancer will be obtained from the published literature. This data will be combined using regression analysis to estimate the preclinical incidence and progression of disease based on Gleason score and PSA.

Task 1.2 Utilizing data from the control arm of the ERSPC, create a model of the characteristics of prostate cancer at diagnosis in a contemporary, unscreened population. We will utilize data provided by investigators from the ERSPC to model tumor and patient characteristics of clinically-diagnosed prostate cancer in the modern era, including age, stage at diagnosis, and Gleason score,

Task 1.3 Utilizing data from a database of men diagnosed in the pre-PSA era, create a model of the progression of clinically localized, conservatively-treated prostate cancer. We have created a database of such men in collaboration with investigators from Örebro, Sweden, that will be used to develop transition probabilities between model health states described in Task 1.1. We will collaborate with Dr. D'Amico in interpretation and analysis of the data, particularly with regard to modeling PSA kinetics.

Task 1.4 Calibrate the model using data from published studies of the natural history of conservatively-treated prostate cancer and recent clinical trials. We will calibrate the model to reproduce target outputs within 5% of pre-selected values. Sources of calibration data for our model will include incidence data from the control arm of the ERSPC and the published literature.

Timeline: The collection and analysis of data from the ERSPC and the Örebro cohort and from the published literature will take 9 months. Construction and calibration of the natural history model will take 15 months. Two manuscripts will be generated: the first will reflect findings from the primary data, and the second will describe the natural history model. I will also take a course during the fall of the first year in order to acquire skills necessary to develop transition probabilities from the published literature.

Outcomes: This task will result in the creation of a natural history model of unscreened, conservatively-treated prostate cancer that will provide data on characteristics of patients at clinical diagnosis and at progression, rates of progression, and prostate cancer specific- and all cause mortality.

Progress report:

The construction of this portion of the model is crucially dependent upon data obtained from the Örebro cohort, as described in Task 1.3. This model will be unique in that it will be able to trace the natural history of prostate cancer in men diagnosed in the pre-PSA era whose prostate cancer has been regraded in the modern era, hence avoiding the concern raised by the fact that Gleason scores have shifted higher over the past 20 years. As described in last year's progress report, during analysis of the data from Örebro during the first 9 months of the grant period, I realized that in our cohort, Gleason score did not correlate with prostate cancer-specific survival. This finding is at odds with the published literature and prompted me to question the accuracy of the Gleason grading performed. A representative selection of pathologic samples was obtained from Örebro and regraded by a pathologist at Massachusetts General Hospital. It was realized that serious errors in Gleason scoring had been made and that as a result, this data was unusable. Therefore, the decision has been made to have all the samples in the cohort regraded. However, in the interim, in working with colleagues in Örebro and at the Harvard School of Public Health, additional patients have been

identified to be added to the patient population. We are therefore still in the process of regrading Gleason samples. It is anticipated that regarding of the pathologic samples will be completed by December 2011. The timeline for both Tasks 1 and 2 will therefore be shifted forward by approximately 18 months. Since the discovery of this complication, my research efforts have therefore been primarily focused on Task 3, as described below.

TASK 2: Compare the clinical effectiveness, cost and cost-effectiveness of PSA screening strategies.

Methods. ***Task 2.1 Vary the biopsy threshold for screening PSA, the interval between screening events, and establish the effect of PSA kinetics prior to diagnosis on screening strategies.*** We will first assess the effect of annual screening varying PSA biopsy thresholds. We will then vary the interval between PSA screening events using these thresholds. These two variables will then be modified simultaneously to identify the screening strategy that maximizes LE. Subsequent analyses will focus on identifying the optimal screening strategy once a PSA velocity has been established. The model will vary PSA velocity, biopsy threshold, and subsequent screening interval simultaneously. Similar analyses will be performed using PSA doubling time.

Task 2.2 For each strategy, establish the lead time and effect on prostate cancer incidence. To quantitate lead time, the difference in time between screen diagnosis and clinical diagnosis of prostate cancer will be calculated. To estimate incidence and overdiagnosis rates, incidence in the presence and absence of screening will be compared.

Task 2.3 Extend the model to include quality of life adjustments (utilities) and costs and use the model to estimate the clinical effectiveness, cost, and cost-effectiveness of each screening strategy.

We will run the model using both community and patient-elicited utilities from the published literature and unpublished results provided by Dr. Murray Krahn[30-33]. Dr. Swan will assist in analysis of these utilities and their incorporation into the model. Costs will be estimated from a societal perspective[48-50]. Costs and QALYs will be discounted. Total cost will be the sum of direct medical costs. Costs will be calculated using data from the medical literature or local institutional cost data and will be expressed in 2008 dollars.

The model will estimate the QALE and costs associated with each screening strategy. The model results will estimate the magnitude of benefit for intermediate and long-term outcomes, costs of care, and incremental cost-effectiveness.

Task 2.4 Identify model parameters likely to cause a shift in model results using sensitivity analysis. We will perform sensitivity analysis on parameters likely to have a significant effect on LE in our model. The model will be run across a literature-derived plausible range of probabilities for selected variables.

Timeline: Modification of the model to assess screening strategies, model calibration, and the calculation of lead time, incidence, and overdiagnosis rates will take approximately one year. Identification of costs, analysis and incorporation of utilities, cost-utility analysis and sensitivity analysis are projected to take nine months. I will take several courses at HSPH during the first two years to acquire the skills necessary for this task. One manuscript will be generated after completion of the screening model to describe the effect of screening on LE in conservatively-treated patients and the lead time and overdiagnosis associated with screening; the second at the completion of the CEA.

Outcomes: This task entails the creation of a PSA screening model that will compare outcomes in screened versus unscreened conservatively-treated men. Outcomes will include LE, QALE, and cost-effectiveness for each strategy and identification of the strategy that maximizes each of these outcomes; secondary outcomes will include lead time, incidence, and overdiagnosis rates for each strategy.

Progress report:

This task, originally planned to be undertaken during months 18-42, will be conducted months 36-60.

TASK 3: Modify the model created in Task 2 to include modern treatment practices to evaluate the clinical effectiveness, cost, and cost-effectiveness of the PSA screening strategies described above.

Methods. ***Task 3.1 Extend the model created in Task 2 to include modern treatment practices.*** We will incorporate modern treatment practices into the model to determine the effect of screening and treatment of screen-diagnosed disease on LE, QALE, and its cost-effectiveness. Treatments and outcomes will be obtained from the published literature and expert opinion, and sensitivity analysis will be performed[7,53,54].
Task 3.2 Extend the model to include quality of life adjustments (utilities) and costs and use the model to estimate the effectiveness, cost, and cost-effectiveness of each screening strategy. In treated men, utilities and costs will be calculated, and effectiveness and cost-effectiveness of each screening strategy will be estimated, as described in Task 2.3.
Task 3.3 Explore the role of future, as-yet-undeveloped diagnostic tests in screening for prostate cancer to establish the test characteristics required in order to identify men with clinically significant disease. The creation of a natural history model will enable us to identify the characteristics of prostate cancer most predictive of outcomes. Decision analytic modeling will highlight predictors of adverse outcomes in our model and will enable us to use them to characterize an "ideal" screening test.
Timeline: Modification of the model to include modern treatment practices and its calibration will take one year. Identification of costs, analysis and incorporation of utilities, cost-utility analysis and sensitivity analysis are projected to take nine months; analysis and comparison of these results with those obtained in Task 2 will take 3 months. Two manuscripts will be produced: the first describing the effect of screening on LE in treated vs. untreated men, the second at the completion of the CEA. Courses I will take to acquire skills necessary for this task will be taken during the second and third years. I will attend seminars and national meetings and continue clinical work with prostate cancer patients throughout the award period.
Outcomes: Outcomes for this task will include LE, QALE, and cost-effectiveness for each screening strategy in men treated for prostate cancer and identification of the screening strategy that maximizes each of these outcomes.

Progress report:
In last year's progress report, we described the Markov Monte Carlo model comparing active surveillance to treatment at diagnosis with radical prostatectomy or radiation therapy using brachytherapy, intensity-modulated radiation therapy, or proton beam therapy. Briefly, a societal perspective was taken with a lifetime horizon. A systematic review of the literature was performed to establish transition probabilities for disease outcomes and for the probabilities of incurring complications of surgery and adverse effects (erectile dysfunction, urinary incontinence, gastrointestinal dysfunction)[1-3]. Utilities were obtained from literature review and from personal communication[4-6], (personal communication, Stewart). Costs were obtained from Medicare reimbursement schedules and included costs of initial treatment, treatment of side effects, and patient time costs. Sensitivity analyses were performed on key parameters. Outcomes included QALE, costs, and cost-effectiveness.

In last year's progress report, I also described an analysis of the comparative effectiveness of active surveillance as compared to initial treatment, without costs. In this study, the QALE benefit of AS was examined in detail. On multiple sensitivity analyses, it was found that the QALE advantage of AS is quite robust: it remained the preferred strategy over initial treatment even if the risk of progressive disease or prostate cancer-specific death on AS was almost doubled, or the risk of side effects of treatment was halved. However, utilities played a key role in establishing the QALE advantage of AS. In particular, the value placed by individuals on being on AS and on having been treated was a major determinant of whether AS was favored. This analysis determined the utility thresholds at which initial treatment would be favored over AS. This work

was submitted to *JAMA* in the summer of 2010 and was published after revision in that journal in December 2010 (please see appendix)[7].

Over the past year, we have extensively revised and expanded the cost-effectiveness model of treatment strategies for low-risk, clinically localized prostate cancer in screened men, as follows:

1) using editorial comments from the review of our *JAMA* article, we restructured the effectiveness component of the model
2) we revised and expanded the cost structure of the model, modifying it to include more detail regarding costs incurred on active surveillance and to reflect one-time vs. recurrent costs, among other alterations.
3) we updated our review of the literature, in particular of studies of active surveillance, to reflect the recent publication of key articles (for example Dr. Klotz' description of his active surveillance cohort)[8]
4) we expanded the model to include men ages from 55-75
5) we structured the model to reflect the recent presentation of data from the PIVOT study, in which men with low risk prostate cancer did not benefit in terms of survival from radical prostatectomy as compared to watchful waiting after 10 years of follow up.

A portion of these results were presented in an oral presentation session at the Society for Medical Decision Making's annual conference in Toronto in October 2010. A manuscript examining the cost-effectiveness of these strategies in men of varying ages is in its final stages of preparation for submission, and a manuscript evaluating the cost-effectiveness of new technologies in treating prostate cancer (such as proton beam therapy and robot-assisted laparascopic radical prostatectomy) is in progress.
Completed abstracts and manuscripts are listed in the Reportable Outcomes section of this report.

In addition to refinements to the preexisting model, with the help of a computer programmer I hired this year, we have translated the cost-effectiveness model from TreeAge into C++, a program more suitable to the larger natural history model. The model structure itself is preserved, as well as the calculated probabilities associated with a) disease outcomes both on active surveillance and after treatment, b) complications of radical prostatectomy, c) side effects of all treatments, and d) utilities associated with health states used in the model. Costs will also be included. The new model has been extensively tested for reproducibility with the original model and has been shown to be consistent.

The completed model described above is specific to men with low-risk prostate cancer (Gleason $\leq$ 3+3; clinical stage $\leq$T2a, PSA <10 ng/mL). Modifications necessary to generalize this model to all men treated after screening will include a review of the literature to establish prostate cancer-specific outcomes for men with intermediate and high-risk disease, outcomes that are expected to be reflected in shorter life expectancies for men with higher-risk disease. It is anticipated that these modifications to the model will require 6 months to complete and will take place from months 54-60 of the grant period, as originally planned.

However, over the course of this year, I have also begun to analyze practice patterns for the treatment of men with biochemical recurrence of prostate cancer after definitive treatment and with metastatic disease. The next step in this project will be to analyze the costs of these treatments.

This analysis, using our institutional CRIS (Prostate Cancer Research Information System) database at Dana-Farber Cancer Institute, along with data from the literature, will provide information regarding costs incurred by patients from recurrence of their disease after treatment to death for use to address Task 3.2[9].

KEY RESEARCH AND TRAINING ACCOMPLISHMENTS

Research Accomplishments:

In summary, work completed on this grant proposal to date has demonstrated that

a) in screen-detected men with low-risk prostate cancer, active surveillance is a cost-effective alternative to initial treatment with radical prostatectomy or radiation therapy (with brachytherapy, intensity-modulated radiation therapy, or proton beam therapy), for men between 55 and 75 years of age at diagnosis.

b) the quality-adjusted life expectancy benefit of active surveillance seen in these men is robust but depends upon the patient preferences, or utilities, associated with being on active surveillance and with having been treated.

Training accomplishments:

a) I have built a Markov Monte Carlo model, acquiring skills including model design, the derivation of probabilities to populate the model, utilities, and costs through regular instruction by my mentor Dr. Michael Barry, Dr. James E. Stahl, Dr. Pamela McMahon.

b) Completion of the Society for Medical Decision Making's Meta-Analysis Course, October 2010

c) Attendance at

ITA Core Seminar, a weekly seminar at ITA with didactic lectures focusing on study design, analysis, and grant-writing, and presentations of ongoing research including decision analysis, cancer outcomes, technology and quality of life assessment.

Lank Center for GU Oncology Seminar, a bi-monthly lecture series during which basic research and recent developments in the diagnosis and treatment of GU cancers are presented.

Lank Center for GU Oncology Journal Club, a monthly presentation of critical articles in genitourinary cancer basic and clinical research.

Dana-Farber/Harvard Cancer Center Outcomes Research Seminar, a weekly seminar at DFCI focusing on study design and analysis and critical review of work in progress.

d) I have continued my clinical training under the guidance of Dr. Philip Kantoff through seeing patients 1.5 days/week and case discussions in both formal and informal settings.

REPORTABLE OUTCOMES

Manuscripts:

Hayes JH, Ollendorf DA, Pearson SD, et al. Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis. *JAMA.* Dec 1 2010;304(21):2373-2380.2.

A second manuscript examining the cost-effectiveness of therapeutic options for low-risk prostate cancer is in the final stages of preparation.

An analysis evaluating the cost-effectiveness of new technologies such as IMRT, proton beam therapy, and robot-assisted laparascopic radical prostatectomy is in progress.

Abstracts July 2010-July 2011:

Hayes JH, Ollendorf DA, Barry MJ, Pearson SD, McMahon PM. A Cost-effectiveness analysis of therapeutic options for low-risk prostate cancer. *Med Decis Making*, January/February 2011; vol. 31, 1: p.E100.

Presentations July 2010-July 2011:

Hayes JH, Ollendorf DA, Barry MJ, Pearson SD, McMahon PM. A cost-effectiveness analysis of therapeutic options for low-risk prostate cancer. Abstract 5418
Oral presentation, Society for Medical Decision Making Annual Meeting, October 2010

Hayes, JH. Active Surveillance vs. Initial Treatment for Low-Risk Clinically Localized Prostate Cancer. Invited Speaker, Cancer Intervention and Surveillance Modeling Network Annual Meeting. NIH, Bethesda, MD. December 2010

Hayes, JH. Author in the Room Teleconference: Active Surveillance Compared With Initial Treatment for Men With Low-Risk Prostate Cancer: A Decision Analysis. Invited Speaker, Institute for Healthcare Improvement and Journal of the American Medical Association, Chicago, IL. January 2011.

Patents and licenses applied for/issued:

None

Degrees obtained that are supported by this training grant:

None

Development of cell lines, tissue or serum repositories:

None

Infomatics such as databases and animal models:

None

Funding applied for based on work supported by this award:

Prostate Cancer Foundation Young Investigators Award.
Applied for and received, grant period July 2010 to July 2013.
The funds from this award are used to pay the salary of a computer programmer who is assisting in the development of the natural history model.

Employment or research opportunities applied for and/or received based on experience/training supported by this grant

None

CONCLUSIONS

In screen-detected men with low-risk prostate cancer, active surveillance appears to be a safe and effective alternative to initial treatment. In this model, the quality of life advantage associated with AS is robust, reflecting the deferred and substantially lower incidence of side effects of treatment experienced by men on AS. AS is associated with significant improvements in QALE even in analyses in which the probability of dying of prostate cancer or of developing progressive disease on AS is increased. However, our finding that the optimal strategy is sensitive to utility weights is evidence that the decision whether to pursue AS must be individualized. In future, models incorporating individual patient utilities may be available to assist patients and their caregivers to estimate the risks and potential benefits of AS prior to making this decision.

Active surveillance is also a cost-effective therapeutic approach in men between the ages of 55 and 75. In this model, active surveillance was associated with an ICER of only $11094/QALY for 65 year old men as compared to brachytherapy, the next most effective strategy, well below the traditional willingness-to-pay threshold of $50-75,000/QALY. The cost-effectiveness of active surveillance as compared to initial treatment is maintained over sensitivity analyses including probability of adverse effects, progressive disease on active surveillance, and utilities. This strategy is a promising one both on an individual and on a societal level, and it is hoped that increasing utilization of this approach will counteract the overtreatment resulting from PSA screening.

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APPENDICES

1. Hayes JH, Ollendorf DA, Barry MJ, Pearson SD, McMahon PM. A Cost-effectiveness analysis of therapeutic options for low-risk prostate cancer. *Med Decis Making*, January/February 2011; vol. 31, 1: p.E100.

Purpose: The optimal therapeutic approach for low-risk clinically-localized prostate cancer (CaP) is unknown: over 50% of screen-detected men are overtreated and treatment is associated with significant side effects (SE). This analysis examines the cost-effectiveness of radical prostatectomy (RP), radiation therapy (IMRT), brachytherapy (BT), proton beam therapy (PBT) and active surveillance (AS) in these men.

Method: A state transition model was constructed and analyzed using Monte Carlo simulation. Men received treatment or AS and incurred SE for 1-2 y and costs until death of CaP/other cause. Men on AS could elect therapy or be treated at progression (both with IMRT). The base case used 65 yo men and included therapy and patient time costs. Transition probabilities and utilities were developed from literature review. Sensitivity analysis on key parameters was performed. Main outcomes were costs (2008US$) and quality-adjusted life-years (QALYs), both discounted at 3%/y, and incremental cost-effectiveness ratios (ICERs).

Result: AS was most effective, providing 8.58 QALYs at a cost of $30422. Compared to RP, AS provided an additional 9.1 mo of QALE at an added cost of $2074 (ICER $2729/QALY). Among initial therapies, BT was most effective and least expensive, providing an additional 3.5 mo of QALE at a cost savings of $2743 vs. RP. IMRT and PBT were more expensive than BT, RP, or AS.

Strategy	Cost($)	Incremental Cost($)	QALYs	Incremental QALYs	ICER
BT	25,606	-	8.11	-	-
RP	28,348	2743	7.82	-0.29	Dominated(D)
AS	30,422	2074	8.58	0.76	$2729/QALY
IMRT	37,808	7386	8.09	-0.88	D
PBT	53,828	16,020	7.96	-0.13	D

Dominated: more expensive and less effective than BT *Alternative Analyses.* AS followed by BT was more effective and less expensive than any initial therapy or AS followed by IMRT. The relative risk of CaP-specific death would have to be 0.6 for therapy vs. AS for QALE to be equal. *Sensitivity Analysis (SA).* AS was most effective on SA including probability of SE, progressive disease on AS and utilities. If IMRT cost was reduced to <$17000 AS was more effective and less expensive than initial therapy.

Conclusion: In this model, AS is associated with higher QALE than initial therapy and carries a minimal additional cost relative to RP or BT. AS should be strongly considered in these patients.

2. Hayes JH, Ollendorf DA, Pearson SD, et al. Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis. *JAMA.* Dec 1 2010;304(21):2373-2380.2.

Active Surveillance Compared With Initial Treatment for Men With Low-Risk Prostate Cancer

A Decision Analysis

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Context In the United States, 192 000 men were diagnosed as having prostate cancer in 2009, the majority with low-risk, clinically localized disease. Treatment of these cancers is associated with substantial morbidity. Active surveillance is an alternative to initial treatment, but long-term outcomes and effect on quality of life have not been well characterized.

Objective To examine the quality-of-life benefits and risks of active surveillance compared with initial treatment for men with low-risk, clinically localized prostate cancer.

Design and Setting Decision analysis using a simulation model was performed: men were treated at diagnosis with brachytherapy, intensity-modulated radiation therapy (IMRT), or radical prostatectomy or followed up by active surveillance (a strategy of close monitoring of newly diagnosed patients with serial prostate-specific antigen measurements, digital rectal examinations, and biopsies, with treatment at disease progression or patient choice). Probabilities and utilities were derived from previous studies and literature review. In the base case, the relative risk of prostate cancer–specific death for initial treatment vs active surveillance was assumed to be 0.83. Men incurred short- and long-term adverse effects of treatment.

Patients Hypothetical cohorts of 65-year-old men newly diagnosed as having clinically localized, low-risk prostate cancer (prostate-specific antigen level $<$10 ng/mL, stage $\leq$T2a disease, and Gleason score $\leq$6).

Main Outcome Measure Quality-adjusted life expectancy (QALE).

Results Active surveillance was associated with the greatest QALE (11.02 quality-adjusted life-years [QALYs]), followed by brachytherapy (10.5 QALYs), IMRT (10.43 QALYs), and radical prostatectomy (10.23 QALYs). Active surveillance remained associated with the highest QALE even if the relative risk of prostate cancer–specific death for initial treatment vs active surveillance was as low as 0.6. However, the QALE gains and the optimal strategy were highly dependent on individual preferences for living under active surveillance and for having been treated.

Conclusions Under a wide range of assumptions, for a 65-year-old man, active surveillance is a reasonable approach to low-risk prostate cancer based on QALE compared with initial treatment. However, individual preferences play a central role in the decision whether to treat or to pursue active surveillance.

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In 2009, 192 000 men were diagnosed as having prostate cancer in the United States. Of these men, 70% will have been classified as having low-risk, clinically localized disease, and more than 90% will have undergone initial treatment.[1-4] Initial treatment choices include surgical resection or radiation therapy. The majority of men experience at least 1 adverse effect of treatment.[5-7]

In the era of prostate-specific antigen (PSA) screening, up to 60% of men diagnosed as having prostate cancer may not require therapy.[8] Results of the European Randomised Study of Screening for Prostate Cancer demonstrated a 20% mortality reduction attributable to screening and treatment; however, 48 additional men needed to be treated to prevent 1 prostate cancer death.[2] It is not currently possible to distinguish patients who require treatment to avoid

For editorial comment see p 2411.

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Table 1. Model Inputs for Disease-Related and Treatment-Related Probabilities

Annual Probabilities	Base-Case Estimate (SD)[a]	Range Used in Sensitivity Analysis
Disease-related probabilities		
Low-risk prostate cancer		
Biochemical recurrence after treatment[5-7]	Year 1, 0.01; lifetime risk, 0.45	Not varied
Progression from biochemical recurrence to metastatic disease[17]	0.05	Not varied
Death due to prostate cancer after development of metastatic disease[18]	0.22	Not varied
Active surveillance		
Progression to Gleason score ≥7[19]	0.0263 (0.007)	0.0132-0.526
Other progression (eg, PSA, DRE)[10,11,19]	0.0268 (0.007)	0.0134-0.536
Electing treatment	0.018 (0.005)	0.009-0.036
Development of metastatic disease prior to treatment	0.008	0.004-0.016
Intermediate-risk prostate cancer (Gleason score ≥7)		
Biochemical recurrence after treatment[20]	Year 1, 0.01; lifetime risk, 0.60	Not varied
Progression from biochemical recurrence to metastatic disease[17]	0.05	Not varied
Adverse effects of treatment		
Short term		
Radical prostatectomy[6]		
Perioperative death	0.0044 (0.00001)	0.0022-0.0088
Major complications[b]	0.0472 (0.0168)	0.0236-0.0944
Minor complications[c]	0.0948 (0.0019)	0.0474-0.1896
Urinary toxicity	0.47 (0.0578)	0.235-0.94
Erectile dysfunction	0.77 (0.0384)	0.385-1
Urethral stricture	0.0344 (0.002)	0.0172-0.0688
IMRT[5,7]		
Urinary toxicity[d]	0.3 (0.0835)	0.15-0.6
Gastrointestinal toxicity	0.18 (0.0506)	0.09-0.36
Brachytherapy[5,7]		
Urinary toxicity[d]	0.29 (0.058)	0.145-0.58
Acute urinary retention	0.1 (0.021)	0.05-0.2
Gastrointestinal toxicity	0.02 (0.001)	0.01-0.04
Active surveillance (biopsy)[21]		
Urosepsis	0.001 (0.0001)	0.0005-0.002
Acute urinary retention	0.026 (0.0049)	0.013-0.052
Long term		
Radical prostatectomy[6]		
Urinary toxicity	0.127 (0.011)	0.0635-0.254
Erectile dysfunction	0.453 (0.021)	0.2265-0.906
IMRT[5,7]		
Urinary toxicity[d]	0.04 (0.02)	0.02-0.08
Gastrointestinal toxicity	0.03 (0.01)	0.01-0.04
Erectile dysfunction	0.124 (0.028)	0.032-0.128
Secondary malignancy	0.0003 (0.00008); 1% lifetime risk beginning 10 y after treatment	0.00015-0.0006
Brachytherapy[5-7]		
Urinary toxicity[d]	0.06 (0.039)	0.025-0.10
Gastrointestinal toxicity	0.01 (0.008)	0.005-0.02
Erectile dysfunction	0.124 (0.028)	0.032-0.128
Secondary malignancy	0.00015 (0.000038); 0.5% lifetime risk beginning 10 y after treatment	0.000075-0.0003

(continued)

prostate cancer morbidity and mortality from those who will die with but not because of their cancer. Active surveillance is an alternative to initial treatment for men with low-risk, clinically localized disease that has the potential to mitigate overtreatment.

Active surveillance is a strategy of close monitoring for carefully selected patients with low-risk prostate cancer. The intent of active surveillance is to avert treatment unless disease progression occurs or a patient chooses treatment, in which case treatment with curative intent is undertaken. The results of several observational cohorts of active surveillance have been promising, but follow-up has been relatively short.[9-13]

We performed a decision analysis to assess the quality-adjusted life expectancy (QALE) of active surveillance compared with initial definitive treatment with radical prostatectomy, intensity-modulated radiation therapy (IMRT), or brachytherapy.

METHODS

We constructed a state transition model analyzed using Monte Carlo simulation with TreeAge Pro Suite 2009, version 1.0.2,[14] to estimate health benefits (QALE) accruing to men with low-risk, clinically localized prostate cancer (PSA <10 ng/mL, stage ≤T2a disease, and Gleason score ≤6).[15] In the model, men are treated at diagnosis or undergo active surveillance. Men enter the model at age 65 years and exit at time of death due to prostate cancer or another cause. The decision tree structure is shown in eFigure 1 (available online at http://www.jama.com).

Initial Treatment

Men in this cohort undergo treatment with IMRT, brachytherapy, or open retropubic nerve-sparing radical prostatectomy. Once treated, men are at risk of recurrence as evidenced by an increase in PSA (biochemical recurrence). If a man develops biochemical recurrence, he is at risk of progression to metastatic disease and death due to prostate cancer or another cause.

Active Surveillance

The active surveillance protocol includes regular physical examinations, PSA measurement, and rebiopsy 1 year following diagnosis and every 3 years thereafter. Treatment is triggered by progression to a Gleason score of 7 or higher, other evidence of progression (eg, PSA doubling time), or patient preference. In the base case, all men who are treated receive IMRT because the majority of men older than 65 years are eligible for IMRT, whereas men with shorter life expectancies or large prostates may not be candidates for radical prostatectomy or brachytherapy, respectively.[16] Men with Gleason score progression receive IMRT with 6 months of androgen deprivation therapy.

The structure of the active surveillance model is identical to that of initial treatment from the point of treatment forward; however, men under surveillance may develop metastases prior to treatment.

Table 1. Model Inputs for Disease-Related and Treatment-Related Probabilities (continued)

Annual Probabilities	Base-Case Estimate (SD)[a]	Range Used in Sensitivity Analysis
Development of genitourinary symptoms		
Erectile dysfunction[22]		
Baseline probability at age 65 y	0.3 (0.075)	Not varied
Development of symptoms (increases with age)	0.015 (0.004)	0.0075-0.03
Urinary obstruction[23]		
Baseline probability at age 65 y	0.3 (0.075)	Not varied
Development of symptoms (increases with age)	0.011 (0.003)	0.0055-0.022

Abbreviations: DRE, digital rectal examination; IMRT, intensity-modulated radiation therapy; PSA, prostate-specific antigen.

[a] With one exception, where standard deviations are provided the parameter was varied (range, 0-1) in probabilistic sensitivity analysis. Parameters a and b were derived from the mean and standard deviation in TreeAge Pro using the following formulas: $a = \text{mean}^2 \times (1 - \text{mean})/(\text{SD}^2)$; $b = \text{mean} \times (1 - \text{mean})/(\text{SD}^2) - a$. The exception was the probability of developing metastatic disease prior to treatment while undergoing active surveillance, which was estimated in probabilistic sensitivity analysis using a uniform distribution.

[b] Major complications include major bleeding, deep vein thrombosis/pulmonary embolus, myocardial infarction/stroke, bowel injury, and major/systemic infection.

[c] Minor complications represent outcomes not typically requiring reexploration or invasive intervention (eg, urinary tract infection, hematoma, ileus).

[d] Urinary toxicity includes irritative voiding symptoms and incontinence.

Model Inputs

Model inputs were estimated from a systematic literature review; probabilities used in the model were generated by random-effects meta-analysis[5-7] (TABLE 1, eAppendix, eFigure 2, eFigure 3, and eTable 1). All initial treatments were assumed to have equivalent disease-related outcomes.[5-7] Men treated initially were assumed to have a relative risk of prostate cancer–specific death of 0.83 compared with men in active surveillance, and threshold analysis was performed to identify the relative risk of prostate cancer–specific death at which the optimal strategy changed. The relative risk of 0.83 was derived from a randomized controlled trial comparing radical prostatectomy to watchful waiting, in which radical prostatectomy was associated with a relative risk of death of 0.65 compared with watchful waiting.[24] This trial included men with more advanced disease than those considered eligible for active surveillance, and only palliative treatment was offered to men in the watchful waiting group whose disease progressed. In the base case, the assumption was made that half of the benefit of treatment seen in this study would be maintained in men undergoing active surveillance.

Age-specific risks of death due to causes other than prostate cancer were based on 2006 US life tables.[25]

Complications and Adverse Effects

Radical Prostatectomy. Complications of radical prostatectomy occur within 30 days of surgery and include perioperative mortality, major complications, and minor complications (Table 1).[5-7] Adverse effects include erectile dysfunction and urinary incontinence and are defined as short-term (occurring and resolving within 90 days of treatment) or long-term (occurring or continuing 90 days to 12 months after surgery and remaining stable after 1 year).

Radiation Therapy. For men undergoing radiation therapy, short-term adverse effects occur and resolve within 90 days of treatment; long-term adverse effects occur within 2 years of treatment and remain stable after 2 years. Adverse effects meet or exceed grade 2 on the Radiation Therapy Oncology Group or Common Toxicity Criteria scales and include short- and long-term urinary symptoms (including irritative voiding symptoms and incontinence), bowel disturbances, and long-term erectile dysfunction (Table 1).[26,27] Men receiving brachytherapy are also at risk of acute urinary retention. Secondary malignancy risks emerge 10 years after radiation and persist for life.[28-34] Men treated with IMRT with androgen deprivation therapy experience erectile dysfunction for the year following androgen deprivation therapy administration.[35]

Active Surveillance. In the base case, patients in active surveillance develop erectile dysfunction and urinary obstructive symptoms at the same rate as age-matched men without prostate cancer in the general population.[22,23] If subsequently treated, they are at the same risk of adverse effects of treatment as men treated initially. Modeled complications of repeat biopsy include urosepsis and acute urinary retention.[21]

Utilities

A utility is a weight assigned to an individual's preference for a particular health state, with a range between 0 (death) and 1 (perfect health). Quality-adjusted life-years (QALYs) are generated when this weight is applied to a year of life in the health state described; ie, a higher QALY reflects a year of life in a preferred health state. In the

Table 2. Model Inputs for Utilities for Health States[a]

Health State	Utility (SD) [Range]
Prostate cancer	
Active surveillance[36]	0.83 (0.24) [0.42-1]
Biochemical recurrence	0.68 (0.26) [0.34-1]
Metastatic cancer	0.12 (0.18) [0.06-0.24]
Treatment of adverse effects	
Impotence	0.88 (0.20) [0.44-1]
Urinary difficulty	0.88 (0.16) [0.44-1]
Urinary incontinence	0.81 (0.30) [0.40-1]
Bowel problems	0.63 (0.32) [0.32-1]
Impotence and urinary difficulty	0.77 (0.24) [0.38-1]
Impotence and urinary incontinence	0.84 (0.23) [0.42-1]
Urinary incontinence and bowel problems	0.64 (0.33) [0.32-1]
Impotence and bowel problems	0.55 (0.35) [0.23-1]
Impotence, urinary incontinence, and bowel problems	0.38 (0.30) [0.19-0.75]
Major complications of radical prostatectomy[b]	0.96 (0.012) [0.48-1]
Minor complications of radical prostatectomy[c]	1
Other health states	
Posttreatment without adverse effects[36]	0.80 (0.24) [0.4-1]
Treatment with radical prostatectomy[d]	0.46 (0.36) [0.23-0.92]
Treatment with radiation therapy[d]	1 [0.5-1]

[a] Utilities are from Stewart et al[37] and unpublished data (Stewart et al; 2009) except as otherwise noted.
[b] Weighted average of disutilities of component complications (major bleeding, deep vein thrombosis/pulmonary embolism, systemic infection, myocardial infarction/cerebrovascular accident, bowel injury) from Sullivan and Ghushchyan.[38]
[c] Because minor surgical complications did not involve significant treatment, no decrement in utility was assigned to these complications.
[d] The treatment with radical prostatectomy utility reflected only the utility for undergoing radical prostatectomy without complications, erectile dysfunction, or urinary symptoms. No utility was found in the literature that reflected only the utility for undergoing radiation therapy without adverse effects; sensitivity analysis was performed on a wide range.

base case, utilities were elicited from men without a diagnosis of prostate cancer using the time–trade-off method, in which individuals are asked to define the amount of time they would be willing to sacrifice to be in a better health state vs a poorer health state (TABLE 2).[36-38] Sensitivity analyses were conducted using patient-derived utilities. In the model, patients maintain posttreatment utilities until death, with the exception of utilities related to short-term adverse effects and erectile dysfunction attributed to androgen deprivation therapy.

Sensitivity, Threshold, and Probabilistic Sensitivity Analyses

We conducted 1-way and multiway sensitivity analyses around key variables (ranges are given in Table 1 and Table 2). Threshold analyses were performed to identify probability and utility values at which the optimal strategy (as defined by the highest QALE) changed. Sensitivity analysis was also performed to assess the effect of discounting on model results (eTable 2).

Probabilistic sensitivity analysis was performed and effectiveness calculated for each strategy from 500 samples consisting of 100 000 individual trials run with unique sets of draws from independent distributions around 45 parameters, including probability of prostate cancer–specific death during active surveillance, complications and adverse effects of treatment, and utilities. Uncertainty around event probabilities and utilities was represented using β distributions (Table 1) except for uncertainty around the probability of developing metastatic disease prior to treatment during active surveillance, which was estimated using a uniform distribution.

RESULTS

Base Case

In men aged 65 years, active surveillance, with IMRT for progression, was the most effective strategy (defined as the strategy associated with the highest QALE) producing 11.02 QALYs. Brachytherapy and IMRT were less effective at 10.5 and 10.43 QALYs, respectively. Radical prostatectomy was the least effective treatment, yielding 10.23 QALYs. The difference between the most and least effective initial treatment was 0.25 QALYs, or 3 months of QALE. In contrast, active surveillance provided 6.2 additional months of QALE compared with brachytherapy, the most effective initial treatment.

In the base case, 61% of men initially followed up with active surveillance underwent definitive treatment during their lifetimes because of progressive disease or patient choice at a median of 8.5 years after diagnosis, similar to recent published experience.[9-11,13,39] The risk of prostate cancer–specific death was 9% for initial treatment and 11% for active surveillance in the model.

Active Surveillance: Evaluation of Key Model Parameters

The results of sensitivity and threshold analyses in which active surveillance yielded a lower QALE than an initial treatment are reported herein. Analyses using patient-derived utilities (eTable 3 and eTable 4) and which varied the probability of disease progression during active surveillance (eTable 5), developing symptoms of disease during active surveillance (eTable 5), adverse effects of treatment (eTable 6), and the utilities associated with symptoms during active surveillance (eTable 7) resulted in QALE estimates favoring active surveillance.

Risk of Prostate Cancer–Specific Death. We conducted a threshold analysis to identify how much greater the risk of prostate cancer–specific death would have to be under active surveillance compared with initial treatment for the 2 approaches to be associated with equal QALE. For QALE to be equal, 15% of men undergoing active surveillance would have to die of prostate cancer as opposed to 9% who received initial treatment, a lifetime relative risk of

death of 0.6 for initial treatment vs surveillance.

Analyses of Utilities. The utility or value assigned by individuals to a particular health state is of central importance in the analysis of QALE. Two utilities were key to determining the favored strategy in the base case: (1) the utility for undergoing active surveillance and being at risk of cancer progression (living under active surveillance) and (2) the utility for having been treated and being at risk of recurrence but not experiencing adverse effects of treatment (posttreatment without adverse effects) (eTable 7 and eTable 8).

FIGURE 1 demonstrates this dependence. The line on the graph represents the points at which the QALE of active surveillance was equal to initial treatment with brachytherapy; the shaded area to the right and below the line represents values of the utility for living under active surveillance at which active surveillance produced higher QALE than initial treatment. For example, if the utility for active surveillance was 0.83 (the base-case value), the posttreatment utility had to be less than 0.88 for active surveillance to remain associated with higher QALE. If the posttreatment utility was 0.8 (the base-case value), the utility for living under active surveillance had to be greater than 0.77 for active surveillance to be favored.

When deciding whether to undergo active surveillance, patients and clinicians must weigh the psychological burden of living with prostate cancer and the disease-specific risk of doing so. We therefore performed a threshold analysis simultaneously varying the utility for active surveillance and the incidence of prostate cancer–specific death to identify at which values of each active surveillance would continue to be favored over initial treatment. FIGURE 2 represents the values of utility for active surveillance and incidence of prostate cancer-specific death at which the QALE generated by the model is equal to initial treatment (with brachytherapy). For example, if the utility for active surveillance was 0.9, active surveillance produced a higher QALE than initial treatment even with a risk of prostate cancer–specific death of up to 19%.

Probabilistic Sensitivity Analysis. Given the considerable uncertainty surrounding the model inputs, we performed a probabilistic sensitivity analysis (TABLE 3). These results reflect the uncertainty surrounding each parameter in the model, including utilities, symptoms during active surveillance, adverse effects of treatment, and risk of prostate cancer–specific death during active surveillance. Although the confidence interval for each strategy is wide, the ranking of strategies and the magnitude of effect difference between the strategies was unaltered when uncertainty was incorporated. Moreover, there was no statistical advantage of any initial treatment over active surveillance.

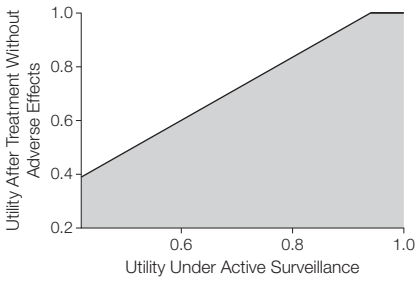
COMMENT

Men aged 65 years at diagnosis followed up with active surveillance received an additional 6.2 months of QALE compared with treatment with brachytherapy, the most effective initial treatment, in the base-case results. This analysis demonstrates that when a broad spectrum of possible disease- and quality of life–related outcomes associated with active surveillance and treatment is taken into account, active surveillance is a reasonable approach to consider in 65-year-old men with clinically localized, low-risk prostate cancer.

However, in the United States, active surveillance is used infrequently for management of prostate cancer. Although 16% to 40% of men newly diagnosed as having prostate cancer meet criteria for active surveillance, less than 10% of eligible men elect this approach.[40,41] Barriers to its use have included concerns about long-term disease outcomes, the perception that most men will ultimately undergo treatment, and concerns about the quality of life of men who elect active surveillance.[42,43]

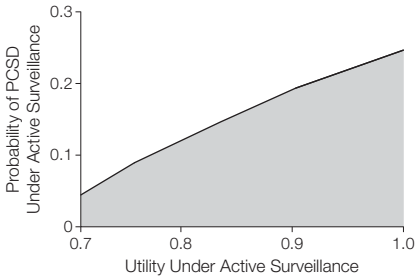
The long-term outcomes of men who undergo active surveillance are poorly characterized. Prospective studies of active surveillance have differing eligi-

Figure 1. Threshold Analysis of Utility for Living Under Active Surveillance and for Having Undergone Treatment Without Adverse Effects



Line indicates point at which quality-adjusted life expectancy of surveillance is equal to initial treatment. Shading indicates active surveillance favored over initial treatment.

Figure 2. Threshold Analysis of Utility for Being Under Active Surveillance and Probability of PCSD Under Active Surveillance



Line indicates point at which quality-adjusted life expectancy of active surveillance is equal to initial treatment. Shading indicates active surveillance favored over initial treatment. PCSD indicates prostate cancer–specific death.

Table 3. Probabilistic Sensitivity Analysis

Strategy	QALYs (95% Confidence Interval)	Incremental QALY
Active surveillance	11.02 (6.94-15.10)	
Brachytherapy	10.80 (5.37-16.23)	–0.22
IMRT	10.63 (5.42-15.89)	–0.17
Radical prostatectomy	10.41 (4.84-15.98)	–0.22

Abbreviations: IMRT, intensity-modulated radiation therapy; QALY, quality-adjusted life-year.

bility criteria and triggers for treatment, complicating the interpretation of results[9-11,13,39] (eTable 9). The relative merits of one set of eligibility criteria and treatment triggers over another for capturing clinically significant disease and minimizing overtreatment have not been established. Recently, Klotz et al[9] published results on the cohort with the longest median follow-up to date, 6.8 years. Thirty percent of the cohort progressed to definitive treatment; outcomes were favorable after short follow-up, with 97.2% 10-year prostate cancer–specific survival and 78.6% overall survival.

Given the uncertainty surrounding long-term outcomes with active surveillance, we analyzed the effect on the results of varying the estimates of prostate cancer–specific death and progressive disease during active surveillance. In the base case, we assumed that the relative risk of prostate cancer–specific death after initial treatment compared with active surveillance was 0.83, half that of radical prostatectomy compared with watchful waiting as reported in a randomized controlled trial.[24] In that trial, men were not screen-detected and in general had higher-risk disease than patients typically followed up with active surveillance, who are offered potentially curative treatment. The relative risk of prostate cancer–specific death was 0.65 (95% confidence interval, 0.45-0.94) for treatment vs watchful waiting in men of all ages; in men older than 65 years, the relative risk was 0.87 (95% confidence interval, 0.51-1.49) and was not significant. We chose 0.83 as the base case assumption of relative risk to approximate a conservative but reasonable risk of prostate cancer–specific death in the absence of a randomized controlled trial comparing treatment to active surveillance. We then performed sensitivity analyses to assess the point at which the QALE advantage of active surveillance could be overcome by a higher risk of prostate cancer–specific death. For active surveillance and initial treatment to be associated with equal QALE, the relative risk of prostate cancer–specific death after initial treatment vs active surveillance would have to be 0.6. Even if choosing active surveillance places men at a substantially higher risk of dying of prostate cancer or the risk of progressive disease on active surveillance is doubled, active surveillance is associated with higher QALE.

Few studies of quality of life in men undergoing active surveillance have been performed, and even fewer have measured utilities for active surveillance health states. However, anxiety in men who have chosen active surveillance or watchful waiting has not been shown to be higher than in men who elect initial treatment.[44-47]

In this analysis, active surveillance was favored over initial treatment for low-risk disease in men aged 65 years at diagnosis, but this result was highly dependent on the utility individuals place on living under active surveillance compared with having been treated.[48] In the base case, the utility for living under active surveillance was 0.83; having been treated without adverse effects of therapy but at risk of recurrence carried a utility of 0.80, 2 values taken from the same population.[36] If these values are varied, the results of the model change significantly. If the utility for active surveillance is raised above 0.94, active surveillance is favored no matter the utility assigned to the posttreatment health state. If the utility for the posttreatment health state is 0.80 (the base-case value), the utility for active surveillance must be greater than 0.77 for active surveillance to be favored. To place this utility in context, a utility of 0.77 is assigned to living with both impotence and urinary difficulty (Table 2). However, there is no posttreatment utility at which initial treatment is favored independent of the utility for living under active surveillance. Figure 1 demonstrates the importance of utilities in the model results but also reflects the central role of patient preference in the decision-making process.

These findings challenge the perception that active surveillance is a reasonable approach only if the risk of prostate cancer–specific death is equal to that seen with initial treatment. We found that as the utility for living under active surveillance increases, the minimal risk of prostate cancer–specific death associated with active surveillance necessary for initial treatment to be favored increases as well (Figure 2). This analysis simulates the decision-making process experienced by patients and physicians, who must weigh disease-specific and psychological risks of active surveillance.

Probabilistic sensitivity analysis indicates the degree to which uncertainty surrounding each variable affects the results as a whole. The uncertainty surrounding the probabilities and utilities used in the model reflects the gaps in the published literature from which we generated the model inputs. We have been conservative in modeling, assuming a high degree of uncertainty in the distribution parameters and no correlation between events, thereby exaggerating the uncertainty in the results. The overlapping confidence intervals seen in this analysis are therefore not unexpected. However, the ranking of strategies and the magnitude of benefit of active surveillance compared with other strategies mirror the base-case results. The contribution of the probabilistic sensitivity analysis, and of this analysis as a whole, lies in the finding that despite substantial uncertainty surrounding this clinical question, active surveillance appears to be a reasonable alternative to initial treatment.

To our knowledge, this is the first decision analysis comparing active surveillance with initial treatment for low-risk prostate cancer. Previous decision analyses have compared watchful waiting with initial treatment.[18,48-52] The most recent decision analysis[48] used probabilities derived from Bill-Axelson et al[53] for the watchful waiting cohort and found that, in contrast to our study, initial treatment was associated with a benefit in QALE for men with low- and medium-risk disease aged 70 years when average, patient-derived preferences were used. How-

ever, as in our study, individual patient preferences were critical in determining the optimal treatment for patients with low-risk disease.

This decision analysis modeled outcomes only for 65-year-old men; therefore, interpretation of these results must be limited to this population. Most studies performed to date in younger men have demonstrated disease-specific outcomes equivalent to older men.[54-58] However, given the uncertainty surrounding long-term outcomes in men followed up with active surveillance, presenting results including younger men would have required extensive sensitivity analysis and discussion surrounding this issue. In addition, this model does not incorporate comorbidities common in older men. Including analyses of younger or older men would have limited the ability to consider the importance of utilities in the outcomes in healthy 65-year-old men, the focus of this analysis.

Additional limitations of this study reflect those in the literature on which model inputs were based. The results of randomized studies comparing active surveillance with initial treatment are expected to emerge over the next few years. A more comprehensive catalog of prostate cancer health states is needed, as is an assessment of the disutility associated with uncertainty among men who choose not to be actively treated.[37] In addition, the use of adjuvant and salvage radiation therapy after radical prostatectomy was not modeled. In this low-risk population, the use of subsequent radiation therapy is relatively rare, and given the magnitude of QALE benefit of active surveillance compared with radical prostatectomy, it is unlikely that including a small survival benefit from subsequent radiation would substantively alter these conclusions.[59-62]

The quality-of-life advantage associated with active surveillance is robust in this model of treatment alternatives for men with clinically localized, low-risk prostate cancer. This benefit reflects the deferred and substantially lower incidence of adverse effects of treatment experienced by men under active surveillance. Active surveillance is associated with significant improvements in QALE even in analyses in which the probability of dying of prostate cancer or of developing progressive disease during active surveillance is increased. However, the finding that the optimal strategy is sensitive to utility weights is evidence that the decision whether to pursue active surveillance must be individualized. Models that incorporate individual patient utilities should be developed to assist patients and their caregivers to estimate the risks and potential benefits of active surveillance before making this decision.

Author Contributions: Dr Hayes had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Hayes, Ollendorf, Pearson, Barry, Stahl, McMahon.
Acquisition of data: Hayes, Ollendorf, Pearson, Stewart, Bhatnagar, McMahon.
Analysis and interpretation of data: Hayes, Ollendorf, Pearson, Barry, Kantoff, Stewart, Sweeney, Stahl, McMahon.
Drafting of the manuscript: Hayes, Ollendorf, Pearson, Barry, Sweeney, Stahl, McMahon.
Critical revision of the manuscript for important intellectual content: Ollendorf, Pearson, Barry, Kantoff, Stewart, Bhatnagar, Stahl, McMahon.
Statistical analysis: Hayes, Ollendorf, Pearson, McMahon.
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Study supervision: Pearson, Barry, Kantoff, Stahl.
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Online-Only Material: The eAppendix, eFigures 1 through 3, and eTables 1 through 9 are available online at http://www.jama.com.
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stances, we do not believe that it would have been appropriate to introduce into the discussion questions about the cost of care.

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CORRECTIONS

Data Corrections: In the Original Contribution entitled "Active Surveillance Compared With Initial Treatment for Men With Low-Risk Prostate Cancer," published in the December 1, 2010, issue of *JAMA* (2010;304[21]:2373-2380), several data points were incorrect. Updated data for QALE and QALYs appear in the first sentence of the abstract results, the IMRT and brachytherapy rows in Table 1, the first paragraph of the Results in the text, the first sentence of the Comment section, and all of Table 3. This article has been corrected online. In addition, data changes were made to the online-only supplemental content in eTables 2 through 8.

Incorrect Data: In the Review titled "Antihypertensive Treatment and Secondary Prevention of Cardiovascular Disease Events Among Persons Without Hypertension: A Meta-analysis," published in the March 2, 2011, issue of *JAMA* (2011; 305[9]:913-922), data were incorrectly reported. In the "composite CVD outcomes" portion of Figure 2, the event numerator in the active group of the SOLVD study should have been 629; the event numerator in the placebo group of the ADVANCE study should have been 136; the total event numerator in the placebo group should have been 3747; and the total event denominator in the placebo group should have been 20 101. This article has been corrected online.

> Invention is one of the great marks of genius; but . . . it is by being conversant with the inventions of others that we learn to invent; as by reading the thoughts of others we learn to think.
>
> —Sir Joshua Reynolds (1723-1792)